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CHARCOAL. See WOOD.

CHELATING AGENTS

A chelating agent, or chelant, contains two or more electron donor atoms that can form coordinate bonds to a single metal atom. After the first such coordinate bond, each successive donor atom that binds creates a ring containing the metal atom. This cyclic structure is called a chelation complex or chelate, the name deriving from the Greek word chela for the great claw of the lobster (1).

Chelation is an equilibrium system involving the chelant, the metal, and the chelate. Equilibrium constants of chelation are usually orders of magnitude greater than are those involving the complexation of metal atoms by molecules having only one donor atom.

Chelating agents may be used to control metal ion concentrations. Chelation complexes usually have properties that are markedly different from both the free metal ion and the chelating agent. Consequently, chelating agents provide a means of manipulating metal ions through the reduction of undesirable effects by sequestration or through creating desirable effects such as in metal buffering, corrosion inhibition, solubilization, and cancer therapy.

Chelates and chelation reactions are abundant in nature, ranging from delicately balanced life processes depending on traces of metal ions to extremely stable metal chelates in crude petroleums. Examples of biochemical processes involving chelates include photosynthesis, oxygen transport by blood, certain enzyme reactions, ion transport through membranes, and muscle contraction. Technological applications include scale removal from steam boilers, water softening, ore leaching, textile processing, food preservation, treatment of lead poisoning, chemical analysis, tissue specific medical procedures, and micronutrient fertilization of agricultural crops.

Structure and Termin I gy

The structural essentials of a chelate are coordinate bonds between a metal atom or a stable oxo cation, M, which serves as an electron acceptor, and two or more

atoms in the molecule of the chelating agent, or ligand, L, which serve as the electron donors. A chelating agent may be bidentate, tridentate, tetradentate, and so on, according to whether it contains two, three, four, or more donor atoms capable of simultaneously complexing with the metal atom. Examples are shown in Figure 1. Molecules having only one donor atom, such as water and dimethylamine, are monodentates and form coordination complexes but not chelates. The principal donor atoms in practical use are N, O, and S, but P, As, and Se also form chelates. Metals are characterized by coordination numbers which correspond to the number of donor atoms bound to the central metal atom in a particular compound. The most common coordination numbers are four and six. Some metals have more than one coordination number, depending on the valence state. The term coordination number also refers, albeit less commonly, to the maximum number of donor atoms to which the metal atom can coordinate.

If the coordination number of M is greater than the number of donor atoms in the ligand L, more than one ligand molecule may combine with the metal to form the complex ML_n as in structure (2) where $n = 2$. Moreover, different chelating molecules can combine with the same metal atom to form species such as $L_mML'_n$. Remaining vacant coordination sites of the metal may also bind monodentate molecules as illustrated in (1) and (3). Solvated metal ions in water or

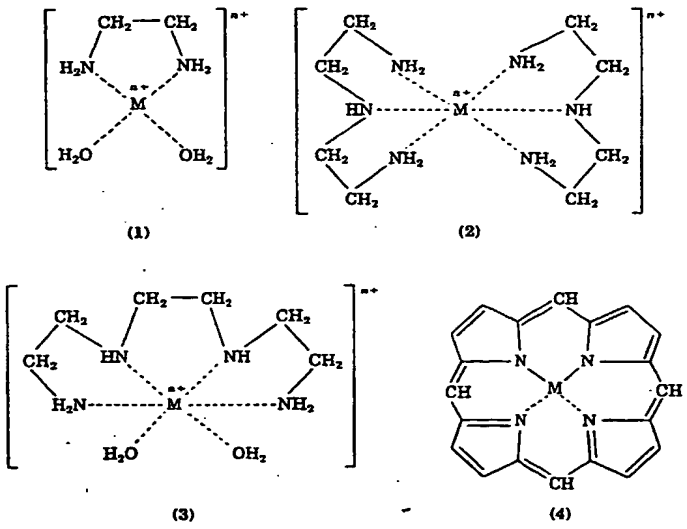


Fig. 1. Types of chelates where (1) represents a tetracoordinate metal having the bidentate chelant ethylenediamine and monodentate water; (2), a hexacoordinate metal bound to two diethylenetriamines, tridentate chelants; (3), a hexacoordinate metal having triethylenetetramine, a tetradentate chelant, and monodentate water; and (4), a porphine chelate. The dashed lines indicate coordinate bonds.

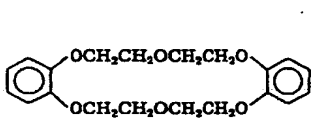
other monodentate solvents are generally solvent coordinated and therefore, chelate formation should be regarded as a displacement of solvent molecules by the donor atoms of the chelating ligand.

Just as a metal can coordinate with more than one chelating molecule, a ligand having enough donor atoms in the proper configuration can bind more than one metal. These metal atoms may be the same or different.

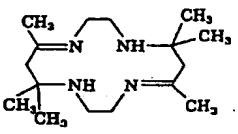
A chelate compound may be either a neutral molecule or a complex ion associated with the appropriate counterions to produce electroneutrality. The formal charge on the complex is the algebraic sum of the charges resulting from any charge on the ligand or ligands and the charge of the metal. The ligand may be neutral or completely or partially ionized before chelation occurs. Changes in the charge of either or both metal atom and chelating agent may occur during the chelating reaction as, for example, by the displacement of hydrogen atoms or ions from the ligand donor atoms, or by an oxidation–reduction reaction between the metal and the chelant. After the chelate is formed, the charge of the complex can also change. Charge change often involves ionization of groups on the ligand that are not involved in the chelate structure, usually as a result of changes in the pH, or by oxidation or reduction of the chelated metal atom.

Most chelating agents are linear or branched chains where the donor atoms are separated by suitable numbers of other atoms to allow the formation of the chelate rings. However, there are also classes of chelating agents where the donor atoms are contained within macrocyclic structures. The spacer atoms complete the chelate rings between pairs of coordinated donor atoms, forming a pattern of fused rings centered about the metal. The porphyrins are examples of this type of chelate, and structure (4) represents chelates of porphine [*101-60-0*], the parent compound of the porphyrins.

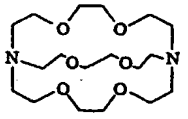
Another group of macrocyclic ligands that have been extensively studied are the cyclic polyethers, such as dibenzo-[18]-crown-6 (5), in which the donor atoms are ether oxygen functions separated by two or three carbon atoms. The name crown ethers has been proposed (2) for this class of compounds because of the resemblance of their molecular models to a crown. Sandwich structures are also known in which the metal atom is coordinated with the oxygen atoms of two crown molecules.



(5)



(6)



(7)

Related to the crown ethers are compounds, such as hexamethyl-[14]-4,11-diene N_4 (6), which differ by the replacement of one or more of the oxygen atoms by other kinds of donor atoms, particularly N or S. Macrocyclic amine and thioether compounds have been synthesized. Compounds having more than one kind of heteroatom in the ring are called mixed-donor macrocycles. The naturally occurring metabolites nonactin [*6833-84-7*] and monactin [*7182-54-9*] have both ether and ester groups incorporated in the macrocyclic structure.

Three-dimensional polymacrocyclic chelating agents are formed by joining bridgehead structures with chains that contain properly spaced donor atoms. For example, bicyclic molecules result from joining nitrogen bridgeheads with chains of ($-OCH_2CH_2-$) groups as in 2.2.2-cryptate (7) (3). Such bicyclic structures form a cavity that holds a metal coordinated to the donor atoms in the surrounding chains. Other groups that are at least trifunctional can serve as bridgeheads, eg, pentaerythritol [*115-77-5*] (see ALCOHOLS, POLYHYDRIC). The donor atoms of the bridges may all be O, N, or S, or the compounds may be mixed donor macrocycles in which the bridge strands contain combinations of these donor atoms. Synthesis, metal binding, and thermodynamic properties of synthetic multidentate macrocyclic complexing agents have been reviewed (4).

Incorporating ligand groups into a cross-linked polymer structure gives the chelate-forming resins that perform ion-exchange functions by chelation. The ligand groups may either be present in the monomer before polymerization, or they may be attached to a preformed polymer by appropriate reactions. Several types are commercially available. Cross-linked styrenedivinylbenzene bonded at the nitrogen atoms to iminodiacetic acid groups is such a polymer.

Compounds Having Chelating Properties

Compounds with chelating properties can be found in almost any class of structures containing two or more donor atoms spatially situated so that they can coordinate with the same metal atom. The chelate rings formed contain four or more members, but for the same donor atoms, the five- or six-membered chelate rings are usually the most stable and most useful. Complexes having chelate rings of more than six members are rare. In the macrocyclic molecules, the stability of the metal complex depends strongly on the relationship between the size of the metal ion and the size of the opening within the crown or the crypt.

Chelating agents may be either organic or inorganic compounds, but the number of inorganic agents is very small. The best known inorganic chelants are polyphosphates. The annual consumption of these compounds exceeds that of all the organic chelating agents combined. Polyphosphates are less expensive than the organics but are hydrolytically unstable at high temperature and pH. Although many hundreds of organic chelating agents are known, only a few members of a few classes of compounds find extensive industrial use. One important class of organic chelating agents is the group of phosphonic acids analogous to the amino- and hydroxycarboxylic acids. These phosphonate chelants possess many of the complexing properties of the inorganic polyphosphates, particularly threshold-scale inhibition, effective at much less than stoichiometric ratios of chelant to metal ion, but unlike the polyphosphates, the phosphonates are stable in water at high temperature and pH.

Table 1 lists a number of chelating agents, grouped according to recognized structural classes. Because systematic nomenclature of chelating agents is frequently cumbersome, chelants are commonly referred to by common names and abbreviations. For the macrocyclic complexing agents, special systems of abbreviated nomenclature have been devised and are widely used. Some of the donor

Table 1. Classes of Chelating Agents

Chelating agent	CAS Registry Number	Molecular formula	Abbreviation
	Polyphosphates		
sodium tripolyphosphate	[*7758-29-4*]	$Na_5P_3O_{10}$	STPP
hexametaphosphoric acid	[*18694-07-0*]	$H_6O_{18}P_6$	
	Aminocarboxylic acids		
ethylenediaminetetraacetic acid	[*60-00-4*]	$C_{10}H_{16}N_2O_8$	EDTA
hydroxyethylethylenediamine-triacetic acid	[*150-39-0*]	$C_{10}H_{18}N_2O_7$	HEDTA
nitrilotriacetic acid	[*139-13-9*]	$C_6H_9NO_6$	NTA
N-dihydroxyethylglycine	[*150-25-4*]	$C_6H_{13}NO_4$	2-HxG
ethylenebis(hydroxyphenylglycine)	[*1170-02-1*]	$C_{18}H_{20}N_2O_6$	EHPG
	1,3-Diketones		
acetylacetone	[*123-54-6*]	$C_5H_8O_2$	acac
trifluoroacetylacetone	[*367-57-7*]	$C_5H_5F_3O_2$	tfa
thenoyltrifluoroacetone	[*326-91-0*]	$C_8H_5F_3O_2S$	TTA
	Hydroxycarboxylic acids		
tartaric acid	[*526-83-0*]	$C_4H_6O_6$	
citric acid	[*77-92-9*]	$C_6H_8O_7$	cit
gluconic acid	[*133-42-6*]	$C_6H_{12}O_7$	
5-sulfosalicylic acid	[*97-05-2*]	$C_7H_6O_6S$	5-SSA
	Polyamines		
ethylenediamine	[*107-15-3*]	$C_2H_8N_2$	en
diethylenetriamine	[*111-40-0*]	$C_4H_{13}N_3$	dien
triethylenetetramine	[*112-24-3*]	$C_6H_{18}N_4$	trien
triaminotriethylamine	[*4097-89-6*]	$C_6H_{18}N_4$	tren
	Aminoalcohols		
triethanolamine	[*102-71-6*]	$C_6H_{15}NO_3$	TEA
N-hydroxyethylethylenediamine	[*111-41-1*]	$C_4H_{12}N_2O$	hen
	Aromatic heterocyclic bases		
dipyridyl	[*366-18-7*]	$C_{10}H_8N_2$	dipy, bipy
o-phenanthroline	[*66-71-7*]	$C_{12}H_8N_2$	phen
	Phenols		
salicylaldehyde	[*90-02-8*]	$C_7H_6O_2$	
disulfopyrocatechol	[*149-46-2*]	$C_6H_6O_8S_2$	Tiron, PDS
chromotropic acid	[*148-25-4*]	$C_{10}H_8O_8S_2$	DNS
	Aminophenols		
oxine, 8-hydroxyquinoline	[*148-24-3*]	C_9H_7NO	Q, ox
oxinesulfonic acid	[*84-88-8*]	$C_9H_7NO_4S$	

Table 1. (*Continued*)

Chelating agent	CAS Registry Number	Molecular formula	Abbreviation
	Oximes		
dimethylglyoxime	[*95-45-4*]	$C_4H_8N_2O_2$	
salicylaldoxime	[*94-67-7*]	$C_7H_7NO_2$	
	Schiff bases		
disalicylaldehyde 1,2-propylenediimine	[*94-91-7*]	$C_{17}H_{18}N_2O_2$	
	Tetrapyrroles		
tetraphenylporphin	[*917-23-7*]	$C_{44}H_{30}N_4$	
phthalocyanine	[*574-93-6*]	$C_{32}H_{18}N_8$	
	Sulfur compounds		
toluenedithiol (Dithiol)	[*496-74-2*]	$C_7H_8S_2$	tdth
dimercaptopropanol	[*59-52-9*]	$C_3H_8OS_2$	BAL
thioglycolic acid	[*68-11-1*]	$C_2H_4O_2S$	
potassium ethyl xanthate	[*140-89-6*]	$C_3H_6OS_2{\cdot}K$	
sodium diethyldithiocarbamate	[*148-18-5*]	$C_5H_{11}NS_2{\cdot}Na$	
dithizone	[*60-10-6*]	$C_{13}H_{12}N_4S$	dz
diethyl dithiophosphoric acid	[*298-06-6*]	$C_4H_{11}O_2PS_2$	
thiourea	[*62-56-6*]	CH_4N_2S	
	Synthetic macrocyclic compounds		
dibenzo-[18]-crown-6	[*14187-32-7*]	$C_{20}H_{24}O_6$	
hexamethyl-[14]-4,11-dieneN$_4$	[*29419-92-9*]	$C_{16}H_{32}N_4$	
(2.2.2-cryptate)	[*23978-09-8*]	$C_{18}H_{36}N_2O_6$	
	Polymers		
polyethyleneimines			PEI
	[*9002-98-6*]	$(C_2H_5N)_x$	
	[*25988-99-2*]	$(C_2H_5N)_x$	
	[*32167-41-2*]	$(C_2H_5N)_n C_8HF_{17}O_2S$	
polymethacryloylacetone	[*25120-51-8*]	$(C_7H_{10}O_2)_x$	
poly(*p*-vinylbenzyliminodiacetic acid)	[*30395-28-9*]	$(C_{13}H_{15}NO_4)_x$	
	Phosphonic acids		
nitrilotrimethylenephosphonic acid	[*6419-19-8*]	$C_3H_{12}NO_9P_3$	NTPO, ATMP
ethylenediaminetetra-(methylenephosphonic acid)	[*1429-50-1*]	$C_6H_{20}N_2O_{12}P_4$	EDTPO
hydroxyethylidenediphosphonic acid	[*2809-21-4*]	$C_2H_8O_7P_2$	HEDP

atoms involved in chelation and the many forms in which they can occur have been reviewed (5).

Nomenclature and Structural Representation

Chelating Agents. Besides the conventional empirical and structural formulas, chelating compounds and chelates are often represented by type formulas, ie, formulas that show only generalized types of structural features. Chelants having proton acid groups may be shown as H_nA or, if partially dissociated, as H_mA^{n-}. Alcohol or phenol groups that lose protons on chelation are shown as $A(OH)_n$. The letter A may be used to represent an entire multidentate ligand molecule or to show only a donor atom as in A–A–A–A for a tetradentate ligand.

For many macrocyclic ligands, simplified names are in common use. For example, crown ether nomenclature consists of four parts: (*1*) the number and type of fused rings on the polyether ring; (*2*) in square brackets the number of atoms in the polyether ring; (*3*) the word crown; and (*4*) the number of oxygen atoms in the macro ring (2). Ligand structures may be represented by any of the conventional means for depicting structure, eg, see structures (5–7).

Chelates. Because of length and complexity, systematic names of chelates are little used except for special purposes, such as where unequivocal referencing is essential. Chelates are named in the literature in a variety of ways. The name of the ligand in a chelate is usually given a suffix -o or -ato if it is a negative group but remains unchanged if the ligand is electrically neutral. Prefixes indicate the number of bound ligand molecules. The central atom is given the name of the metal, or a derivative name having the suffix -ate, eg, cuprate and ferrate, if the complex is negatively charged. Oxidation states of the metals are indicated by Roman numerals, eg, iron(III), and ionic charges are shown as part of the name by Ewens-Bassett numbers, eg, (2+) or (1−).

Chelates are often named merely as a complex, eg, cadmium complex with acetylacetone. A common practice in the literature is to give the symbol of the central atom and an abbreviation for the ligand with or without an indication of ionic charges, oxidation states, structure, or counterions, as in the following: Pb-EDTA, $Cacit^-$, $Cu(en)_2$, Co(II)-(phen), $[Cu(dipy)_3]SO_4$, $[Ru(dipy)_2(en)]^{2+}$, and $Na[Co(acac)_3]$. Ligand abbreviations are given in Table 1.

Several ways of representing chelates are shown in Figure 2. Structures (8) and (9) represent bidentates; structures (10) and (11), tetradentates; and structures (12) and (13) the same hexadentate. Square brackets, evident in structures (9)–(11), may be used to emphasize that the structure is a complex ion, but brackets are not a requirement. The sum of charges shows that structure (12) is also a charged (1−) complex; structure (8) is neutral. In structure (13), which is used to show spatial arrangements, the curved lines represent chains of unspecified length connecting the donor atoms. Note that the aromatic rings in (9) sterically prevent the sulfo groups from chelating with the central metal.

For the many details of constructing or interpreting structures and systematic names, the literature on nomenclature and indexing (6) can be consulted. Systematic nomenclature is illustrated by the *Chemical Abstracts* name of the sodium iron(III) EHPG chelate: sodium [[*N*,*N*'-1,2-ethanediylbis[2-(2-hydroxy-

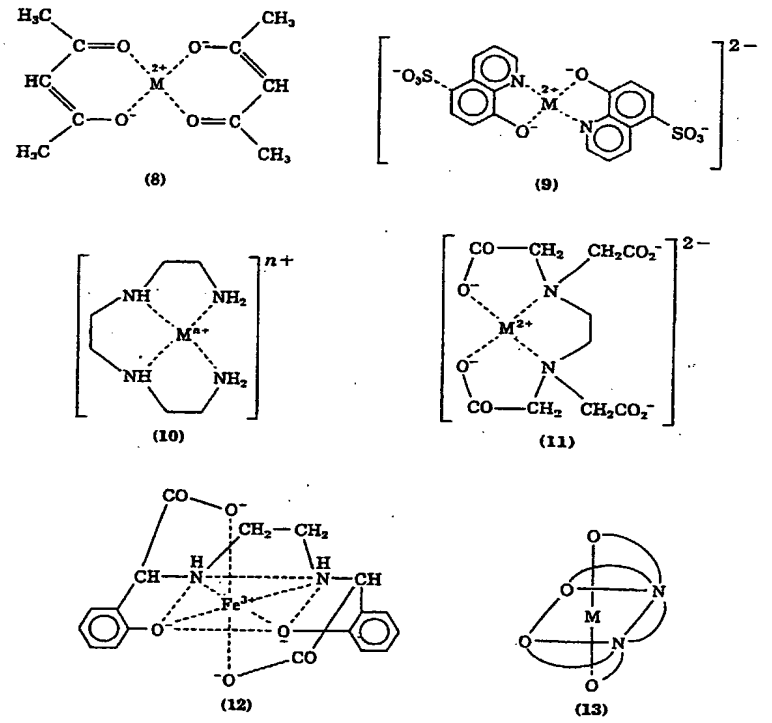


Fig. 2. Structural representations of chelates where (8) corresponds to $M(acac)_2$; (9) to ML_2^{2-}, L = 5-sulfo-8-hydroxyquinoline; (10) to M-Trien; (11) to a tetracoordinate metal bound to the hexadentate ligand EDTA; and (12) to the Fe(III) chelate of EHPG. Structure (13), which emphasizes the spatial arrangement of the donor atoms, also represents the chelate in (12).

phenyl)glycinato]](4-)-*N,N',O,O',O²,O²'*]ferrate(1-) [*16455-61-1*]. The ferrate anion (12) [*20250-28-6*] and the potassium salt [*22569-56-8*] are also listed in *Chemical Abstracts* (7).

The Chelation Reaction

Chelat F rmation Equilibria. In homogeneous solution the equilibrium constant for the formation of the chelate complex from the solvated metal ion and the ligand in its fully dissociated form is called the formation or stability constant.

Whereas the ligand displaces solvent molecules coordinated to the metal, these solvent molecules do not generally enter into the equations. When more than one ligand molecule complexes with a metal atom, the reaction usually proceeds stepwise. For a metal having a coordination number of six and a bidentate chelating agent, the equations representing the equilibria are

$$M + L \rightleftharpoons ML \qquad K_1 = \frac{[ML]}{[M][L]} \tag{1}$$

$$ML + L \rightleftharpoons ML_2 \qquad K_2 = \frac{[ML_2]}{[ML][L]} \tag{2}$$

$$ML_2 + L \rightleftharpoons ML_3 \qquad K_3 = \frac{[ML_3]}{[ML_2][L]} \tag{3}$$

$$\textit{overall: } M + 3\,L \rightleftharpoons ML_3 \qquad K = \frac{[ML_3]}{[M][L]^3} \tag{4}$$

where the square brackets represent concentrations in units of molarity. The overall stability constant is the product of the step stability constants, ie, $K = K_1K_2K_3$, and is often designated by β. Protons displaced from a ligand in the chelation reaction may be shown, as in equation 5, where H_2A^{2-} represents the divalent anion of a multidentate ligand such as EDTA.

$$M^{2+} + H_2A^{2-} \rightleftharpoons MA^{2-} + 2\,H^+ \qquad k = \frac{[MA^{2-}][H^+]^2}{[M^{2+}][H_2A^{2-}]} \tag{5}$$

Such a reaction is the sum of an acid dissociation reaction

$$H_2A^{2-} \rightleftharpoons A^{4-} + 2\,H^+ \qquad K_a = \frac{[A^{4-}][H^+]^2}{[H_2A^{2-}]} \tag{6}$$

and the reaction of chelate formation from the fully dissociated form of the ligand

$$M^{2+} + A^{4-} \rightleftharpoons MA^{2-} \qquad K = \frac{[MA^{2-}]}{[M^{2+}][A^{4-}]} \tag{7}$$

where K is the chelate formation constant, K_a is the overall acid dissociation constant for the two stages, and $k = KK_a$.

Experimentally determined equilibrium constants are usually calculated from concentrations rather than from the activities of the species involved. Thermodynamic constants, based on ion activities, require activity coefficients. Because of the inadequacy of present theory for either calculating or determining activity coefficients for the complicated ionic structures involved, the relatively few known thermodynamic constants have usually been obtained by extrapolation of results to infinite dilution. The constants based on concentration have usually been determined in dilute solution in the presence of excess inert ions to maintain constant ionic strength. Thus concentration constants are accurate only under conditions reasonably close to those used for their determination. Beyond these conditions, concentration constants may be useful in estimating probable effects

and relative behaviors, and chelation process designers need to make allowances for these differences in conditions.

Stability constants for a number of industrially important metals and some widely used chelating agents are given in Table 2. Extensive listings of stability constants are available (8). The practical significance of formation constants is that a high log K value means a large ratio of chelated to unchelated or free metal when equivalent amounts of metal and ligand are present. From the values shown in Table 2, it is apparent that the concentration of free metal ion can range from relatively large to very low depending on the chelant.

Many experimental approaches have been applied to the determination of stability constants. Techniques include pH titrations, ion exchange, spectrophotometry, measurement of redox potentials, polarimetry, conductometric titrations, solubility determinations, and biological assay. Details of these methods can be found in the literature (9,10).

Displacement Equilibria. Species in solution are generally in formation–dissociation equilibrium, and displacement reactions of any given metal or ligand by another are possible. Thus,

Table 2. Concentration Formation Constants of Metal Chelates[a]

	Log K						
					NTA		
Metal ion	STPP	Citric acid	EDTA	EDTPO	Log K_1	Log K_2	Log K_1K_2
V(III)[b]			25.9				
Fe(III)		10.9	25.1		15.9	9.9	25.8
In(III)			25.0		15.0	9.6	24.6
Th(IV)			23.2		12.4		
Hg(II)			21.8		12.7		
Cu(II)	8.7	6.1	18.8	23.21	12.7	3.6	16.3
Ni(II)	6.7	4.8	18.6	16.38	11.3	4.5	15.8
Y(III)			18.1		11.4	9.1	20.5
Pb(II)		5.7	18.0		11.8		
Zn(II)	7.6	4.5	16.5	18.76	10.5		
Cd(II)		4.2	16.5		10.1	4.4	14.5
Co(II)	6.9	4.4	16.3	17.11	10.6		
Fe(II)	2.5	3.2	14.3		8.8		
Mn(II)	7.2	3.4	14.0		7.4		
V(II)			12.7				
Ca(II)	5.2	3.5	10.7	9.36	6.4		
Mg(II)	5.7	2.8	8.7	8.43	5.4		
Sr(II)	4.4		8.6		5.0		
Ba(II)	3.0		7.8		4.8		
rare earths			15.1–20.0		10.4–12.5		

[a]STPP = sodium tripolyphosphate; NTA = nitrilotriacetic acid; EDTA = ethylenediaminetetraacetic acid; EDTPO = ethylenediaminetetra(methylenephosphonic acid) (see Table 1).
[b]The oxovanadium(IV) ion, VO^{2+}, forms a complex with EDTA having log K = 18.8.

$$ML + M' \rightleftharpoons M'L + M \quad (8)$$

or

$$ML + L' \rightleftharpoons ML' + L \quad (9)$$

If the stability constants for ML and M'L are K and K', respectively, then for the exchange shown in equation 8, the equilibrium constant is K_x.

$$K_x = \frac{[M][M'L]}{[ML][M']} = \frac{K'}{K} \quad (10)$$

The extent of displacement depends on the relative stabilities of the complexes and the mass action effect of an excess of M'. For equivalent total amounts of M and M', K_x must be on the order of 10^4 for 99% complete displacement to occur. Similar considerations apply for the displacement of L from ML by L'. The situation is quite analogous to the familiar competition of two bases for the hydrogen ion.

If the metals or ligands involved in a displacement reaction form chelates where type formulas are different, the exchange equilibrium constant is the simple ratio of the formation constants of the chelates. Rather, for the reaction

$$2\,ML + M' \rightleftharpoons 2\,M + M'L_2 \quad (11)$$

the equilibrium constant $K_x = K'/K^2$ assuming K and K' are the respective formation constants of ML and $M'L_2$. The proper evaluation of K_x can be derived for each particular case.

Metal exchange is the mechanism by which many foods, such as shortenings, shellfish, and dairy products, are stabilized against deleterious effects of trace metals by the addition of $Na_2CaEDTA$ ($\log K = 10.7$). Copper ($\log K = 18.8$) and iron ($\log K = 25.1$) displace calcium and become sequestered so that the remaining concentration of free iron or copper ions is too low for catalytic effects to occur at significant rates (11). Ligand exchange occurs when ascorbic acid [*50-81-7*] bound to copper ($\log K = 1.57$) is displaced by EDTA, stabilizing this vitamin by disrupting an oxidation mechanism (12). Dyes and bleaches are similarly protected in the textile industry (13) (see FOOD ADDITIVES; DYES AND DYE INTERMEDIATES; BLEACHING AGENTS).

The addition of a chelating agent to a solution of two or more metal ions leads to an order of metal ion complexation that is regulated by the displacement equilibrium constants. If the objective is to bind only a particular ion, then enough chelant to combine with the target ion and all the other ions that are capable of displacing the target ion should be added. For any particular chelating agent under similar solution conditions, a displacement series of metal ions can be assembled by calculating the K_x values from series of stability constants such as those in Table 2. For selective complexation of one metal in the presence of another, a chelating agent with sufficiently different stability constants for the two metals is necessary so that K_x becomes large. For example, beryllium occurs at the bottom of a displacement series with NTA allowing this metal to be recovered

as the hydroxide by pH adjustment of an ore processing solution; all of the interfering metals remain sequestered by chelation (14). Additionally, because other metals present cannot displace iron in an iron–EHPG chelate, the chelate can be used in highly calcareous soils to supply iron as a trace nutrient in agriculture (15).

Selectivity for a single metal of a group is the basis of a solvent extraction process for the recovery of copper (qv) from low concentration ore leach solutions containing high levels of iron (qv) and other interfering metals (16).

Rates of Reaction. The rates of formation and dissociation of displacement reactions are important in the practical applications of chelation. Complexation of many metal ions, particularly the divalent ones, is almost instantaneous, but reaction rates of many higher valence ions are slow enough to measure by ordinary kinetic techniques. Rates with some ions, notably Cr(III) and Co(III), may be very slow. Systems that equilibrate rapidly are termed kinetically labile, and those that are slow are called kinetically inert. Inertness may give the appearance of stability, but a complex that is apparently stable because of kinetic inertness may be unstable in the thermodynamic equilibrium sense.

Factors Affecting Stability. A characteristic of chelation distinguishing it from monodentate metal coordination is the increased stability from ring formation of the resultant chelate complex. For equal numbers of similar coordinated donor atoms, as in amine complexes compared to chelates of ethylenediamine, eg, $M(RNH_2)_2$ vs M(en) or $M(RNH_2)_4$ vs $M(en)_2$, the stability constants of the chelates are from one to several orders of magnitude greater than those of the monodentate complexes. The greater stability of the chelates is largely the result of an increase in entropy resulting from an increase in the number of free molecules, usually solvent or other monodentate ligand, liberated as the chelate is formed. This extra stabilization produced by the ring formation is called the chelate effect.

Many parameters influence the stability of chelates. Several of the stability factors common to all chelate systems are the size and number of rings, substituents on the rings, and the nature of the metal and donor atoms. In the macrocyclic complexes, the degree to which the size of the metal ion fits the space enclosed by the macro rings is a significant factor. In chelation, five- and six-membered rings are most stable: coordination angles on the metal atoms prohibit the formation of three-membered rings, and ring closure is improbable for rings having more than seven members. In these latter systems, coordination in linear chains is a competing reaction. Formation of each additional ring by the same ligand contributes extra stability from the entropy effect of displacing coordinated solvent molecules. Substituents on a ring may also produce steric hindrance, or otherwise alter the availability of the donor atom electrons for coordination.

The alkaline and rare-earth metals, and positive actinide ions, generally have greater affinity for $-O^-$ groups as electron donors. Many transition metals complex preferentially with enolic $-O^-$ and some nitrogen functions. Polarizability of the donor atoms correlates with stability of complexes of the heavier transition metals and the more noble metal ions.

In any series of chelates, the stability constants are usually influenced by more than one of the parameters that are known to affect chelate stability. The data in Table 3 illustrate some of these relationships: the calcium complexes containing EDTA and homologues decrease in stability as the size of the chelate ring

Table 3. Ring Effects on Complex Stability

Ligand, L	Complex formula	Ring size	Number of rings	Number coordinated donor atoms	Log K^a		
EDTA, $n = 2^b$	CaL	5			10.5		
homologue, $n = 3^{b,c}$	CaL	6			7.1		
homologue, $n = 4^{b,d}$	CaL	7			5.2		
homologue, $n = 5^{b,e}$	CaL	8			4.6		
					Cu(II)	Ni(II)	Co(II)
$H_2NCH_2COOH^f$	ML	5	1	2	8.6	6.2	5.2
$HN(CH_2COOH)_2^g$	ML	5	2	3	10.6	8.2	7.0
$N(CH_2COOH)_3$	ML	5	3	4	12.7	11.3	10.6
					Log K_1	Log K_2	Log K^h
$H_2NC_2H_4NH_2$	CuL	5	1	2	10.72		
	CuL_2	5	2	4		9.31	20.0
$H_2N(CH_2)_3NH_2^i$	CuL	6	1	2	9.77[j]		
	CuL_2	6	2	4		7.1	16.9[j]
$HN(C_2H_4NH_2)_2^k$	CuL	5	2	3	15.9		
	CuL_2	5	2	4		5.4	21.3
$(H_2NC_2H_4NHCH_2)_2$	CuL	5	3	4	20.5		

[a] Ref. 9.
[b] Formula is $(HOOCCH_2)_2N(CH_2)_nN(CH_2COOH)_2$.
[c] Propylenedinitrilotetraacetic acid [*1939-36-2*], $C_{11}H_{18}N_2O_8$.
[d] Tetramethylenedinitrilotetraacetic acid [*1798-13-6*], $C_{12}H_{20}N_2O_8$.
[e] Pentamethylenedinitrilotetraacetic acid [*1798-14-7*], $C_{13}H_{22}N_2O_8$.
[f] Glycine [*56-40-6*], $C_2H_5NO_2$.
[g] Iminodiacetic acid [*142-73-4*], $C_4H_7NO_4$.
[h] Log K = Log K_1K_2.
[i] 1,3-Propanediamine [*109-76-2*], $C_3H_{10}N_2$.
[j] Ref. 10.
[k] *N*-2-Aminoethyl-1,2-ethanediamine [*111-40-0*], $C_4H_{13}N_3$.

formed by the metal and the two coordinating nitrogen atoms increases. The aminoacetic acid series shows the stability gained from the formation of additional rings on a single-ligand molecule. And the copper–polyamine series shows the combined effects of ring size, number of rings for similar donor atoms, and whether the rings are formed by one or more ligand molecules.

pH Effects. Being Lewis bases, the donor atoms of chelating agents react with Lewis acids such as metal and hydrogen ions. In the pH range of aqueous solutions, most of the well-known chelating agents exist as an equilibrium mixture of both protonated and unprotonated forms. Metal ions compete with hydrogen ions for the available donor atoms, and therefore, simultaneous equilibria exist that are treated mathematically by the simultaneous equations for the formation constants of the chelates and the acid dissociation constants of the chelating agents.

In aqueous systems, water is a competing ligand, and its dissociation into hydrogen and hydroxyl ions must often be considered in the system of simultaneous equilibria (see HYDROGEN-ION ACTIVITY). In nonaqueous solvents, similar

treatment is possible with appropriate modifications for the acidity in those systems. The pH leveling effect of water affects and limits the acid dissociation behavior of chelating agents in aqueous systems. However, coordination with certain metals in aqueous solution can result in loss of a proton from aliphatic -OH and $-NH_2$ groups.

Consider the equilibria in an aqueous system composed of a bidentate ligand HA, eg, the enol form of acetylacetone, and a tetracoordinate metal M^{2+}, structure (8). The equations are

$$HA \rightleftharpoons A^- + H^+ \qquad K_a = \frac{[H^+][A^-]}{[HA]} \tag{12}$$

$$M^{2+} + 2\,A^- \rightleftharpoons MA_2 \qquad K = \frac{[MA_2]}{[M^{2+}][A^-]^2} \tag{13}$$

giving the relation

$$[M^{2+}] = [H^+]^2 \times \frac{[MA_2]}{[HA]^2} \times \frac{1}{KK_a^2} \tag{14}$$

Equation 14 shows that an increase in acidity of the solution increases the concentration of uncomplexed metal, which must result from the displacement of M^{2+} from MA_2, causing a simultaneous decrease in the ratio of complexed to free ligand $[MA_2]/[HA]$. The opposite effects result upon decreasing the acidity. This behavior occurs in the pH range where appreciable amounts of both HA and A^- coexist. Outside this range the ligand is present almost entirely as either HA or MA_2 and A^-, and the system is essentially independent of pH.

Chelating agents that are polybasic acids give two or more hydrogen ions per molecule. The four stages of dissociation of EDTA, eg, are represented by the equations

$$H_4A \overset{-H^+}{\rightleftharpoons} H_3A^- \overset{-H^+}{\rightleftharpoons} H_2A^{2-} \overset{-H^+}{\rightleftharpoons} HA^{3-} \overset{-H^+}{\rightleftharpoons} A^{4-} \tag{15}$$

These equilibrium constants K_1, K_2, K_3, and K_4 are known (10). The pK values for the four dissociation steps as well as the proportions of the species present in aqueous solution as a function of pH are shown in Figure 3. The reaction of Na_2EDTA and M^{2+}, represented by equation 5 and noting that $KK_3K_4 = k$, give

$$[M^{2+}] = [H^+]^2 \times \frac{[MA^{2-}]}{[H_2A^{2-}]} \times \frac{1}{KK_3K_4} \tag{16}$$

which is of the same form as equation 14. In general, for the reaction

$$[M^{z+}] + H_nA^{y-} \rightleftharpoons [MA^{z-y-n}] + n\,H^+ \tag{17}$$

the equation for the concentration of free metal is

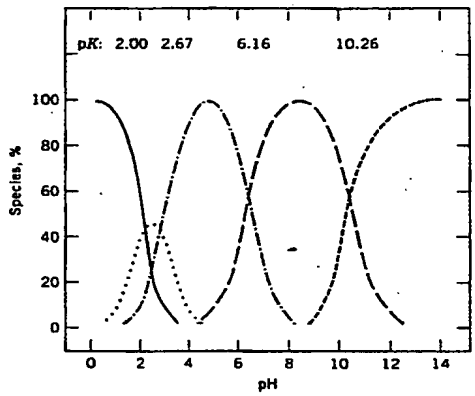


Fig. 3. Distribution of ionic species of EDTA as a function of pH where (——) represents H_4A, (·····) H_3A^-, (——) H_2A^{2-}, (— —) HA^{3-}, and (----) A^{4-}.

$$[M^{x+}] = [H^+]^n \times \frac{[MA^{x-y-n}]}{[H_nA^{y-}]} \times \frac{1}{KC} \tag{18}$$

where K is the formation constant (eq. 7) of MA^{x-y-n} and C is the product of the n stepwise acid dissociation constants involved. Taking the negative logarithm of both sides of the equation and letting $-\log [M^{x+}] = pM$, the equation becomes

$$pM = n\ pH + \log \frac{[H_nA^{y-}]}{[MA^{x-y-n}]} + \log KC \tag{19}$$

The corresponding generalized form for equation 14 is

$$pM = n\ pH + \log \frac{[HA]^n}{[MA_n^{x-n}]} + \log KK_{a^n} \tag{20}$$

In both cases n is the number of hydrogen ions displaced in the formation of the complex. In solutions where the ratio of free chelating agent to complex, $[H_nA^{y-}]/[MA^{x-y-n}]$, is held constant, the slopes of the curves pM vs pH are equal to n in the region where H_nA^{y-} is the principal form of the chelating agent.

The displacement of hydrogen ions by a metal ion from a protonated form of the chelating agent (eq. 17) generates an autogenous pH that depends on the base strength of the counterions of the metal salt. The pH of the solution can become quite low if these counterions are those of a strong acid, eg, Cl^- or SO_4^{2-}. However the pH of chelate solutions can be controlled by the use of compatible buffers, and the chelating agent itself can sometimes serve as the pH buffer if one of its acid dissociation stages occurs in the desired pH range.

The variation of pM with pH according to equation 17 is shown in Figure 4 for EDTA and Cu(II) and EDTA and Mn(II) at three different ratios of free chelant to metal chelate, $[H_nA^{y-}]/[MA^{z-y-n}]$. The pM value at any pH indicates the concentration of the free aquo metal ion in equilibrium with the chelate. From pH 2 to 6, the free form of the EDTA is H_2A^{2-}, and because two protons are displaced by the metal on chelation, the slope of the curves is two. The slope changes to one from pH 6 to 10 where the EDTA is present as HA^{3-} and only one proton is displaced. Above pH 10, the chelates are formed from the fully dissociated chelant, A^{4-}, no hydrogen ions are displaced, the slope of the curves is zero, and pM is independent of pH up to the pH of the intersection of the solid lines with the dashed lines for the same metal. Up to pH 10, the rise of pM with pH shows the increasing degree of metal binding as competition by hydrogen ions for the chelant is decreased. Cu(II) and Mn(II) form insoluble metal hydroxides to which the following applies at equilibrium in aqueous solution:

$$M^{2+} + 2\,OH^- \overset{K_{sp}}{\rightleftharpoons} M(OH)_2\,(s) \qquad K_{sp} = [M^{2+}][OH^-]^2, \quad K_w = [H^+][OH^-] \qquad (21)$$

and from these

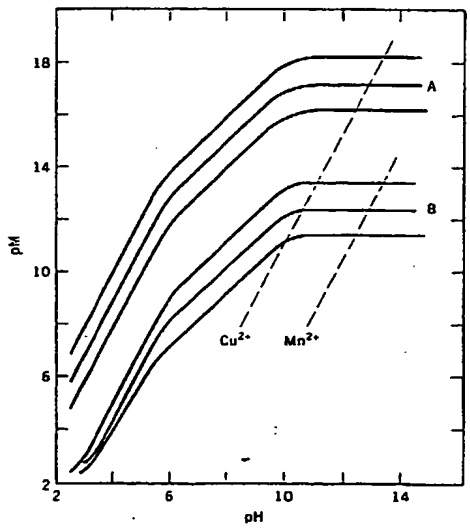


Fig. 4. pM vs pH for A: Cu(II), and B: Mn(II) EDTA chelates. For each family of curves, the lowest curve represents 1%; the second, 10%; and the top curve, 100% of free ligand species in excess of the amount needed to form the metal chelate. Broken lines represent solid–solution equilibria for corresponding metal hydroxides. See equation 22.

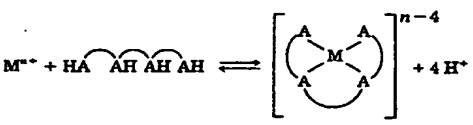
$$pM = 2\ pH + \log (K_w^2/K_{sp}) \quad (22)$$

The dashed lines in Figure 4 are plots of equation 22 for Cu^{2+} and Mn^{2+} and indicate the concentration of the aquo metal ions in equilibrium with the solid hydroxides as function of pH. At any pH where the solid curve is above the dashed line for the same metal, the EDTA is holding the unchelated metal ion concentration at a value too low for the precipitation of the solid hydroxide. Relatively large quantities of the metal can thus be maintained in solution as the chelate at pH values where otherwise all but trace quantities of the metal would be precipitated. In Figure 4, this corresponds to pH values where pM of the dashed curves is 4 or greater. At the pH of intersection of the solid and dashed lines for the same metal, the free metal ion is in equilibrium with both the solid hydroxide and the chelate. At higher pH the hydroxyl ion competes more effectively than the chelant for the metal, and only a trace of either the chelate or the aquo metal ion can exist in solution. Any excess metal is present as solid hydroxide.

The more stable the chelate, the higher the pM that it can maintain, and the higher the pH required to precipitate the metal hydroxide. From equation 22 it can be seen that the smaller the solubility product K_{sp}, ie, the more insoluble the metal hydroxide, the higher the pM that a chelant must maintain to prevent precipitation. The stability constant of the Fe(III)–EHPG complex (12), is so large (10^{35}) that iron is not precipitated even in strongly alkaline solutions.

If instead of hydroxyl ion the precipitating agent is the anion of an acid stronger than or comparable in strength to the chelating agent, the metal salt may be insoluble at low pH where the chelant is protonated but not the precipitant anions, and soluble at higher pH where the complexing form of the ligand is relatively more available. Solutions of oxalate, EDTA, and Ca(II) show this behavior; Figure 5 shows the relationships of pM to pH. The solid lines give pM for the Ca–EDTA system, and the dashed lines represent the calcium oxalate [*563-72-4*], CaC_2O_4, solubility. As in Figure 4, at pH values where the dashed lines are above the solid lines, the metal is present almost entirely as the insoluble salt. To the right of the intersections of dashed and solid lines the metal is almost entirely chelated, and the solid salt phase cannot exist.

Titration Behavior. Protonated chelating agents exhibit titration behavior typical of their respective acidic groups, eg, carboxyl phenolic hydroxyl, ammonium, or sulfhydryl moieties, if they are titrated with bases where the cations have a very weak or no tendency to form chelates. In the presence of a metal ion that coordinates with the donor atom of one of these acidic groups, hydrogen is displaced by the metal, and the acid strength of the group appears to be enhanced. The hydrogen ion concentration is then higher than in the absence of the metal. Strongly chelated metal ions can increase the acidity of an acidic group by several orders of magnitude. With A representing donor groups, which may be the same or different, the release of hydrogen ions is shown schematically by



(23)

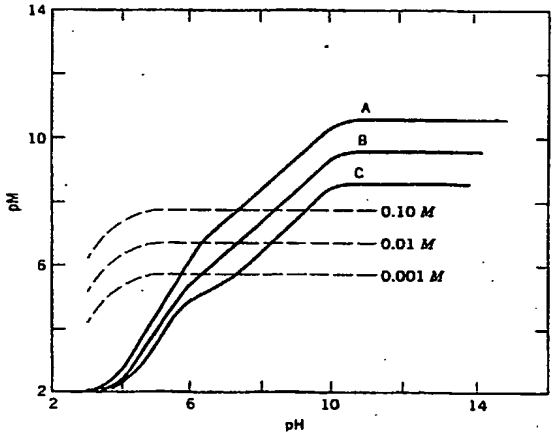


Fig. 5. pM vs pH for M = Ca(II), L = EDTA, in the presence of excess oxalate. Solid lines A, B, C represent 100%, 10%, and 1% excess EDTA, respectively. Broken lines indicate solid–solution equilibria of calcium oxalate in the presence of dissolved oxalate.

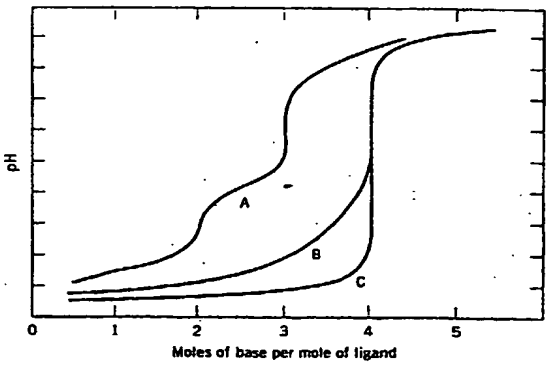


Fig. 6. Base titration of H_4A chelant: A, free acid without coordinating metal; B, in the presence of a metal of intermediate coordinate strength; and C, in the presence of a strongly chelated metal.

In the absence of metal coordination the compound H_4A_4 would titrate as a typical tetrabasic acid having a stepwise titration curve as shown in Figure 6. Upon strong chelation, all four protons are displaced and base titration resembles that of a typical strong acid at four times the equivalent concentration. This statement is in agreement with equation 19, which shows that pM can be large (low concentration of free metal) at low pH if K is large (strong chelation).

If metal chelation is intermediate in strength, the chelation of the groups that are last to coordinate to the metal may not do so to completion at the low pH generated by the hydrogen ions released from the first groups to coordinate. Then, in accordance with equation 19, because K is smaller, the completion of the chelation reaction, as shown by the reduction of the metal ion concentration to a low value (high pM), may not occur until a higher pH is attained where more A-groups are available to the metal. The curve of pH vs base added thus rises sooner than the curve for strong chelation, resembling the titration curve of a weak acid and reflecting the lower apparent acid strength resulting from weaker coordination. The intermediate curve of Figure 6 shows this effect of weaker chelation.

Titration of the hydrogen ion liberated from a strong chelating agent is used to determine the concentration of metal ions in solution. The strength of chelation can also be determined from these data.

Deprotonation of enols of β-diketones, not considered unusual at moderate pH because of their acidity, is facilitated at lower pH by chelate formation. Chelation can lead to the dissociation of a proton from as weak an acid as an aliphatic amino alcohol in aqueous alkali. Coordination of the O atom of triethanolamine to Fe(III) is an example of this effect and results in the sequestration of iron in 1 to 18% sodium hydroxide solution (Fig. 7). Even more striking is the loss of a proton from the amino group of a gold chelate of ethylenediamine in aqueous solution (17).

Another group of chelants that form stable chelates at high pH because of metal–alkoxide coordination are the sugar acids, such as gluconic acid [*526-95-4*], $C_6H_{12}O_7$ (18). Utility for this group is found in high alkalinity bottle washes and other cleansers (19).

Metal Buffering. The equation for the formation constant of the reaction

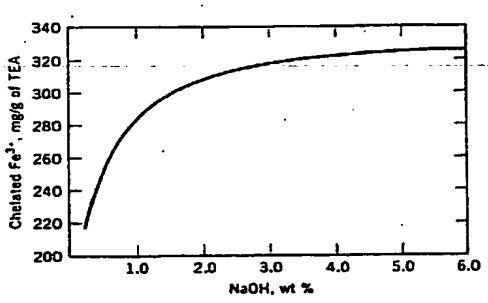


Fig. 7. Chelation of iron by triethanolamine (TEA) in aqueous sodium hydroxide. Courtesy of The Dow Chemical Company.

$$M^{n+} + L^{m-} \overset{K}{\rightleftharpoons} ML^{n-m} \tag{24}$$

can be rearranged to give

$$\frac{1}{[M^{n+}]} = \frac{K[L^{m-}]}{[ML^{n-m}]} \tag{25}$$

from which, on taking logarithms and defining $pM = -\log [M^{n+}]$,

$$pM = \log \frac{[L^{m-}]}{[ML^{n-m}]} + \log K \tag{26}$$

The concentration of the metal ion can be controlled by adjusting the ratio of the concentrations of free ligand and metal chelate. If both species are present in appreciable amounts, moderate changes in either concentration have little effect on the ratio. The concentration of the metal ion can thus be buffered in a manner analogous to the buffering of pH by the presence of a weak acid and its anion

$$pH = \log \frac{[A^-]}{[HA]} + pK_a \tag{27}$$

In the equation for pM, log K appears instead of pK because K is a formation constant, the reciprocal of the chelate dissociation constant, which is analogous to the acid dissociation constant K_a.

By choice of chelating agents, and thus log K, pM can be regulated over a wide range. Two or more metals may be selectively buffered at different concentrations by a single chelating agent having different stability constants for the metals. Selective buffering of one metal to a low concentration in the presence of other metals is termed masking. It is the ability to maintain a nearly constant concentration of metal ions at almost any level of concentration that is the basis of many of the commercial uses of chelating agents. The buffering capacity may be used to supply metal ions at a definite concentration as in electroplating (qv) and in nutrient media (see MINERAL NUTRIENTS), or to remove or sequester metal ions in cleaning baths where the fresh stock entering the bath continually introduces additional amounts of metals.

The effect of pH on metal buffering is shown by equations 19 and 20. If a constant pH is imposed on a system by a hydrogen ion buffer, variations in pM are controlled only by variations in the ratio of the free and metal-bound forms of the ligand, and of course by the characteristics of the ligand. The free form of the ligand is the acid form of its acidic dissociation stage at the imposed pH, ie, HA or H_nA^{y-}. If the acid groups of the chelating agent are fully dissociated at the pH of the buffer, no hydrogen ions are displaced when chelation with the metal occurs, no dissociation constants of the ligand are involved, n in the equations is essentially zero, and pM is independent of pH. Equations 19 and 20 then reduce to the form of equation 26.

Solubilization. The solubility product of a slightly soluble salt determines the concentration of metal ion that can be present in solution with the anion of that salt. For the salt MX the solubility product is

$$K_{sp} = [M^{n+}][X^{n-}] \quad (28)$$

from which is obtained

$$pM = \log [X^{n-}] - \log K_{sp} \quad (29)$$

The presence of a sufficiently strong chelating agent, ie, one where K in equation 26 is large, keeps the concentration of free metal ion suppressed so that pM is larger than the saturation pM given by the solubility product relation (eq. 29) and no solid phase of MX can form even in the presence of relatively high anion concentrations. The metal is thus sequestered with respect to precipitation by the anion, such as in the prevention of the formation of insoluble soaps in hard water.

Deposits of an insoluble salt can be dissolved as a salt of the metal chelate.

$$MX\,(s) + L^{m-} \overset{K_s}{\rightleftharpoons} [ML^{n-m}] + X^{n-} \quad (30)$$

In the presence of the chelating agent and the insoluble salt, MX, pM of the solution is subject to both the metal buffering and the solubility equilibria. Equating the right-hand sides of the equations 26 and 29 and rearranging gives

$$\log [X^{n-}] = \log \frac{[L^{m-}]}{[ML^{n-m}]} + \log KK_{sp} \quad (31)$$

As the dissolving of the salt progresses $[X^{n-}]$ is approximately equal to $[ML^{n-m}]$, and both represent the amount of MX dissolved. Substituting $[ML^{n-m}]$ for $[X^{n-}]$ in equation 31 gives

$$2 \log [ML^{n-m}] = \log [L^{m-}] + \log KK_{sp} \quad (32)$$

for the equilibrium concentrations for the process. If $KK_{sp} = 1$, $\log KK_{sp} = 0$, then $[ML^{n-m}] = [L^{m-}]^{1/2}$, and the amount of MX solubilized is equal to the square root of the amount of excess chelating agent required, which is an amount that is in the practical range. A dilution–efficiency effect can be calculated from this relationship. If the amount of MX dissolved gives only a 0.1 M solution of $[ML^{n-m}]$, the excess ligand concentration is 0.01 M and almost 90% of the total amount of ligand is effective in solubilizing salt deposit. However, for $[ML^{n-m}] = 1.0\ M$ an equal concentration of excess ligand is required and solubilization to 2.0 M requires 4.0 M excess ligand, giving efficiencies of 50 and 33%, respectively. If for economic reasons the chelating agent must be recovered, dilution is a disadvantage, and dilution and efficiency must be compromised. If the stability constant K is large enough, equation 32 shows that only small amounts of the chelating agent in excess of that bound to the metal are required to dissolve a given amount of the deposit.

The product KK_{sp} is equal to the equilibrium constant K_s for the reaction shown in equation 30. It is generally considered that a salt is soluble if $K_s > 1$. Thus sequestration or solubilization of moderate amounts of metal ion usually

becomes practical as K_s approaches or exceeds one. For smaller values of K_s, the cost of the required amount of chelating agent may be prohibitive. However, the dilution effect may allow economical sequestration, or solubilization of small amounts of deposits, at K_s values considerably less than one. In practical applications, calculations based on concentration equilibrium constants can be used as a guide for experimental studies that are usually necessary to determine the actual behavior of particular systems.

The K_s values for some common scale deposits and nitrilotriacetic acid (NTA), which is an effective agent for solubilizing $CaSO_4$ and $CaSiO_3$ ($K_s > 1$), are shown in Table 4. For removal of $CaCO_3$ deposits, a stronger Ca(II) chelating agent would be required. A large cleaning business that services industry is based on the aminocarboxylic acid chelants.

Electrochemical Potentials. The oxidation potential of a solution containing a metal in two of its valence states, M^{x+} and M^{x+n}, is given by

$$E = E^0 - \frac{RT}{nF} \ln \frac{[M^{x+n}]}{[M^{x+}]} \tag{33}$$

In the presence of a chelating agent, the concentrations of the two forms of the metal are buffered according to the simultaneous equations

$$[M^{x+n}] = \frac{[M_{ox}L]}{K_{ox}[L]} \text{ and } [M^{x+}] = \frac{[M_{red}L]}{K_{red}[L]} \tag{34}$$

where $M_{ox}L$ and $M_{red}L$ are the chelates of the oxidized and reduced forms of the ions and K_{ox} and K_{red} are the respective formation constants. Substituting these values in the potential equation gives

$$E = E^0 + \frac{RT}{nF} \ln \frac{K_{ox}}{K_{red}} - \frac{RT}{nF} \ln \frac{[M_{ox}L]}{[M_{red}L]} \tag{35}$$

The first two terms of the right-hand side of the equation are sometimes combined and expressed as $E^{0\prime}$, which is called the standard oxidation potential for the chelate system. If the chelation is strong and the ligand is in excess, the metal would be almost entirely in the chelated forms, and $[M_{ox}L]$ and $[M_{red}L]$ would essentially be equal to the total concentrations of the oxidized and reduced forms of the metal. If, as is usual, the oxidized form is the more strongly chelated

Table 4. K_s values for NTA and Calcium Salts[a]

Salt	K_{sp}	K_s
$CaSO_4$	6.1×10^{-5}	152
$CaSiO_3$	6.6×10^{-7}	1.65
$CaCO_3$	8.7×10^{-9}	0.022

[a] Formation constant $K = 2.5 \times 10^6$.

($K_{ox} > K_{red}$), the oxidation potential of a system is increased by the addition of the chelant.

In electrodeposition, the reduced form of the metal is the elemental form M, x = 0, and there is no chelated M in solution. Neglecting activity coefficients, the reversible potential is

$$E = E^0 - \frac{RT}{nF} \ln [M^{x+}] \quad (36)$$

By buffering the metal ion concentration using a chelant, E can be adjusted to and stabilized at values that give desirable properties to the deposit. Selective buffering can sequester the properties of interfering ions or can be used to regulate the potentials of two or more ions to approximately the same value in order to effect codeposition.

Applications

Three features of chelation chemistry are fundamental to most of the applications of the chelating agents. The first and probably the most extensively used feature is the control of free metal ion concentration by means of the binding–dissociation equilibria. The second, often called the preparative feature, is that in which the special properties of the chelate itself provide the basis of the application. The third feature comprises displacement reactions: metal by other metal ions, chelant by chelant, and chelant by other ligands or ions. An application may be termed defensive if an undesirable property in a process or product is mitigated, or aggressive if a new and beneficial property is induced.

Concentration Control. Sequestration, solubilization, and buffering depend on the concentration control feature of chelation. Traces of metal ions are almost universally present in liquid systems, often arising from the materials of the handling equipment if not introduced by the process materials. Despite very low concentrations, some trace metals produce undesirable effects such as coloration or instability.

Sequestration. The suppression of certain properties of a metal without removing it from the system or phase is called sequestration. Sequestration is invaluable in controlling trace ion effects. Chelation produces sequestration mainly by reducing the concentration of free metal ion to a very low value by converting most of the metal to a soluble chelate that does not possess the properties to be suppressed. A sufficiently large stability constant in the medium of the application is required, and the sequestering agent must not cause any undesirable change that would render the system unsuitable for its intended purpose.

The largest single use for sequestration is probably the control of water (qv) hardness. Chelating agents are used to prevent the formation of precipitates in a wide variety of aqueous systems such as washing solutions of soaps (qv) and detergents, boiler feed water (20), fabric (21) and paper (qv) processing solutions (22), preparations of cosmetics (qv) and pharmaceuticals (qv), photographic developing solutions, chemical process water, beverages, and foodstuffs (18). Oil-

soluble sequestrants suppress metal-catalyzed development of rancidity, gum formation in fuels, and other oxidative degradations (23). In fabric bleaching, catalytic decomposition of bleaching agents (qv) is reduced, and tenderizing of fabrics is minimized by the sequestration of metals that catalyze the reaction of the bleach with the material (24). In dyeing, metal contaminants that cause spotting, off-color shades, and decomposition of the dyes are sequestered (25). Brightness reversion in paper pulp is diminished (26), and iron is removed in the caustic washing step of the preparation of photographic and other special grades of paper. Discoloration of leather (qv) by metal-tannin complexes is prevented. Chelants are used in many metal treating operations such as phosphatizing, alkaline derusting, and etching (see METAL SURFACE TREATMENTS). Poisoning by metal ions in mammals is also treated by sequestration. Other examples can be found in the literature on sequestration and chelation.

Solubilization. Causing the constituents of a phase that is normally insoluble to dissolve in the medium is termed solubilization. Chelation solubilization depends on the formation of a chelate having groups that confer solubility in the medium and a stability sufficient to sequester the metal ion to a concentration (pM) that can exist in the presence of the associated counterions. Usually solubilization into an aqueous phase is thought of in connection with chelation. The donor atoms involved in the chelation may be sufficiently hydrophilic to produce a soluble species, as in structures (10) and (12). If the organic group is large, more hydrophilic groups may be required for water solubility. Oxine is a well-known precipitant, but its sulfonated derivative, shown in structure (9) (Fig. 1), is a solubilizer in water. A neutral chelation complex, such as structure (8), may be solubilized in organic media. The macrocyclic chelates have solubility in both aqueous and organic media as a result of their ionic nature and the largely organic character of the complex.

Dissolving hardness scale from the surfaces of boilers, heat exchangers, and piping (see PIPING SYSTEMS) is probably the largest industrial example of solubilization (27). The cleaning of films from dairy equipment and reusable beverage bottles is also a significant use (19). Deposits on processing tanks that are unique to a particular industry, such as paper, textiles (qv), metal treating, or photography (qv), are often removed by solubilization. Prevention of metal deposition by sequestration is usually preferred where possible because solubilization is sometimes slow and can lead to costly down time. Chelants are used in recovery of metals from ores (28) and in cleaning oxide films from metals in preparation for surface treatments (29). Chelation solubilization is especially useful for cleaning up radioactive contamination.

Macrotetrolides of the valinomycin group of electrically neutral antibiotics form stable 1:1 complexes with alkali metal ions that increase the cation permeability of some biological and artificial lipophilic membranes. This solubilization process appears to have implications in membrane transport research (30) (see ANTIBIOTICS, PEPTIDES).

Buffering. If addition or removal of an appreciable amount of a metal ion produces only a relatively small change in the concentration of that ion in a solution, the solution is buffered with respect to the ion. Metal ions are buffered by chelants of various strengths, ie, stability constants, in a manner exactly analogous to the buffering of hydrogen ions by bases of various strengths.

Chelation buffering is particularly useful in supplying micronutrient metal ions to biological growth systems at controlled, very low concentrations (31). At the very small subtoxic concentrations required for some metals, the amount present would ordinarily soon be depleted, but using the buffer, a reserve supply of the metal as its chelate is available over long periods with automatic control of the concentration. Examples of this kind of use are found in microorganism cultures in closed, controlled systems and in field use in agriculture in open environments (32). The metal concentration can be held at optimum values in electroplating, and chelates have supplied the metal in electroless depositions.

Control of concentrations enables simultaneous deposition of metals in alloy plating. Increasing attention is being given to the use of chelants to replace cyanide in electroplating baths. Chelants are used to control the activity of redox polymerization catalysts by buffering the metal ions participating in the mechanism. Buffering of the metal is produced by having appreciable amounts of both the chelant and the chelate present simultaneously. The pM is determined mainly by the stability constant of the chelate, and within the region of this primary regulation over a small practical range, by the ratio of chelant and chelate concentration.

Special Properties of Chelates. Some of the principal applications of the preparative feature of chelation depend on the solubility properties, color, or catalytic effects of the chelates. Selection of a chelant to form a chelate that is soluble in the medium enables the solubilization of mineral deposits, pipe and boiler scale, films on surfaces, constituents of ores, and similar insoluble materials. Chelates having suitable solubilities can be designed to concentrate a metal into a particular phase by extraction from water into an organic solvent, by binding to a liquid but water-insoluble chelant, by precipitation of the chelate as a solid phase, or by ion exchange onto an insoluble, solid, chelating resin. Color and color fastness in some dyeing processes depend on the properties of chelates. The phthalocyanine [*574-93-6*] pigments (qv) are intensely colored, insoluble chelates. The color of chelates is the basis for many analytical procedures. Catalytic effects may result from a chelate, or chelation of the reactant may itself be part of the mechanism of catalysis by a metal. In biological systems the properties of some enzymes and vitamins (qv) involve chelation, and the activities of chlorophyll and hemoglobin are associated with their chelate structures.

In photography, specially designed chelates suppress or release metal ions to start or stop reactions at appropriate stages in processing sequences, sensitize or desensitize substances to radiation, function in optical and multiplex recording systems, and replace the less environmentally suitable ferricyanide for bleaching (33). Chelates have been used in the preparation of superconducting compounds (34) and as cross-linking agents in fracturing fluids and plugging gels for subterranean formations (35).

Catalysis. In catalysis (qv), the importance of coordination between ligands and metals has long been recognized. The special properties of chelating ligands are especially evident in asymmetric syntheses catalyzed by chelates of an asymmetric ligand, such as in the homogeneous hydrogenation of double-bond functions by a chelate of cobalt and the chiral ligand quinine [*130-95-0*], $C_{20}H_{24}N_2O_2$ (36). In another application, a cobalt chelate is used as an oxygen carrier in the sweetening of gasoline by oxidation of mercaptans.

Chelation is a feature of much research on the development and mechanism of action of catalysts. For example, enzyme chemistry is aided by the study of reactions of simpler chelates that are models of enzyme reactions. Certain enzymes, coenzymes, and vitamins possess chelate structures that must be involved in the mechanism of their action. The activation of many enzymes by metal ions most likely involves chelation, probably bridging the enzyme and substrate through the metal atom. Enzyme inhibition may often result from the formation by the inhibitor of a chelate with a greater stability constant than that of the substrate or the enzyme for a necessary metal ion.

Many reactions catalyzed by the addition of simple metal ions involve chelation of the metal. The familiar autocatalysis of the oxidation of oxalate by permanganate results from the chelation of the oxalate and Mn(III) from the permanganate. Oxidation of ascorbic acid [*50-81-7*], $C_6H_8O_6$, is catalyzed by copper (12). The stabilization of preparations containing ascorbic acid by the addition of a chelant appears to be negative catalysis of the oxidation but results from the sequestration of the copper. Many such inhibitions are the result of sequestration. Catalysis by chelation of metal ions with a reactant is usually accomplished by polarization of the molecule, facilitation of electron transfer by the metal, or orientation of reactants.

Chelation itself is sometimes useful in directing the course of synthesis. This is called the template effect (37). The presence of a suitable metal ion facilitates the preparation of the crown ethers, porphyrins, and similar heteroatom macrocyclic compounds. Coordination of the heteroatoms about the metal orients the end groups of the reactants for ring closure. The product is the chelate from which the metal may be removed by a suitable method. In other catalytic effects, reactive centers may be brought into close proximity, charge or bond strain effects may be created, or electron transfers may be made possible.

The crown ethers and cryptates are able to complex the alkali metals very strongly (38). Applications of these agents depend on the appreciable solubility of the chelates in a wide range of solvents and the increase in activity of the co-anion in nonaqueous systems. For example, potassium hydroxide or permanganate can be solubilized in benzene [*71-43-2*] by dicyclohexano-[18]-crown-6 [*16069-36-6*]. In nonpolar solvents the anions are neither extensively solvated nor strongly paired with the complexed cation, and they behave as naked or bare anions with enhanced activity. Small amounts of the macrocyclic compounds can serve as phase-transfer agents, and they may be more effective than tetrabutylammonium ion for the purpose. The cost of these macrocyclic agents limits industrial use.

Precipitation and Extraction. The processes of extraction and precipitation comprise transferring the metal into another phase. If the ligand charges neutralize those of the metal ion, the complex becomes a neutral molecule. As the size of the hydrophobic part of the ligands increases, the neutral chelates become less soluble in water and precipitate when enough chelate is present to exceed the solubility. Some ligands precipitate certain metals essentially quantitatively. These materials are used for analytical methods and for recovery of metals from ores or from waste streams. Oxine (8-hydroxyquinoline) is a well-known precipitating agent. Selective and successive precipitations are used in the separation and recovery of the rare-earth elements. Passivation of metals by many organic corrosion inhibitors may involve the formation of an insoluble chelate film with

the oxide on the surface or with the metal itself (39) (see CORROSION AND CORROSION INHIBITORS).

A special kind of transfer of metal ions to a solid phase is found in chelating resins, which are similar to ordinary cation-exchange resins except that they have chelating groups in place of the salt-forming moieties. The behavior of the two kinds of resins is similar except that the special effects of the chelation equilibria must be considered. An important use of chelating resins is for the preconcentration of metal ions from such media as seawater, body fluids, and geological materials in which concentration is exceedingly small, so that these ions may be detected or determined analytically (40). Chelating resins may be used functionally in process streams (41).

If a neutral chelate formed from a ligand such as acetylacetone is sufficiently soluble in water not to precipitate, it may still be extracted into an immiscible solvent and thus separated from the other constituents of the water phase. Metal recovery processes (see MINERAL RECOVERY AND PROCESSING), such as from dilute leach dump liquors, and analytical procedures are based on this phase-transfer process, as with precipitation. Solvent extraction theory and many separation systems have been reviewed (42).

Displacement. In many of the applications of chelating agents, the overall effect appears to be a displacement reaction, although the mechanism probably comprises dissociations and recombinations. The basis for many analytical titrations is the displacement of hydrogen ions by a metal, and the displacement of metal by hydrogen ions or other metal ions is a step in metal recovery processes. Some analytical pM indicators function by changing color as one chelant is displaced from its metal by another.

The pH effect in chelation is utilized to liberate metals from their chelates that have participated in another stage of a process, so that the metal or chelant or both can be separately recovered. Hydrogen ion at low pH displaces copper, eg, which is recovered from the acid bath by electrolysis while the hydrogen form of the chelant is recycled (43). Precipitation of the displaced metal by anions such as oxalate as the pH is lowered (Fig. 4) is utilized in separations of rare earths. Metals can also be displaced as insoluble salts or hydroxides in high pH domains where the pM that can be maintained by the chelate is less than that allowed by the insoluble species (Fig. 3).

Rare earths have been separated by elution from ion-exchange resins with chelates of iron, manganese, and cadmium. In another separation, a band of rare earths on an ion-exchange resin was eluted with a chelant and the eluate was passed over an ion-exchange bed loaded with copper. The copper displaced the rare-earth metals that deposited on the second bed. In a solution mining process, a leach solution of $Na_2CaEDTA$ and sodium bicarbonate exchanges Ca for Cu, and the copper is then displaced by lime and the leach solution is regenerated (28). In using chelated chromium in leather tanning, the chromium is captured from the chelant by the collagen in the hide.

The calcium form of EDTA instead of free EDTA is used in many food preparations to stabilize against such deleterious effects as rancidity, loss of ascorbic acid, loss of flavor, development of cloudiness, and discoloration. The causative metal ions are sequestered by displacing calcium from the chelate, and possible

problems, such as depletion of body calcium from ingestion of any excess of the free chelant, had it been used, are avoided.

Medical Uses. A significant usage of chelation is in the reduction of metal ion concentrations to such a level that the properties may be considered to be negligible, as in the treatment of lead poisoning. However, the nuclear properties of metals may retain their full effect under these conditions, eg, in nuclear magnetic resonance or radiation imaging and in localizing radioactivity.

In the treatment of poisoning by lead or other metal ions, higher concentrations of chelant can be safely obtained in humans by administering $Na_2CaEDTA$ rather than Na_4EDTA. The metal ion is bound by displacing small amounts of Ca^{2+} that the body can tolerate. Use of Na_4EDTA would result in calcium chelation and thus serious depletion of calcium in the body fluids (44). Removal of iron in Cooley's anemia is accomplished by using chelants that are relatively specific for iron (45).

Bifunctional chelating agents are capable of being covalently attached to an antibody having specificity for cancer or tumor cell epitopes or antigens (see CHEMOTHERAPEUTICS, ANTICANCER). Radioactive metal complexes of such antibody–chelant conjugates are useful in diagnostic, eg, imaging, and therapeutic (irradiation) applications as a means of delivering the radioactive metal to a cancer or tumor cell or to a specific tissue or location (46). Technetium-99m chelates are the most widely used agents in nuclear medicine for diagnostic imaging of the brain, liver, kidneys, and skeleton. Chelants commonly used include diethylenetriaminepentaacetic acid [*67-43-6*], 1-hydroxyethylidene-1,1-diphosphonic acid [*2809-21-4*], and glucoheptonate (47). Organophosphonic acid chelates of the radioactive isotopes samarium-153 and rhenium-186 have shown promise in bone cancer therapy (48). Gadolinium(III) complexes have been used to enhance the nuclear magnetic resonance images of cerebral tumors (49).

Environmental, Health, and Safety

The primary industrial chelating agents are essentially environmentally benign and nontoxic under the conditions incidental to normal handling and use. With these, eye irritation is mainly a function of the acidity or alkalinity of the form of the product and its solubility. However, use of nitrilotriacetic acid (NTA) is regulated in some jurisdictions. In medical uses the effects of the chelating agents on metal ion balances in the body tissues must be accommodated. Some of the commercial compounds used in smaller amounts as chelants, such as oxalic acid [*144-62-7*], are toxic, however. The hazards of using any chelant should be determined prior to use.

Solutions of iron chelates can be used to remove hydrogen sulfide and oxides of sulfur and nitrogen in industrial gas scrubbing processes (41,50,51) before flue gases are released to the atmosphere.

Economic Aspects

Production and price estimates for the principal industrial chelating agents are given in Table 5. The list is dominated by sodium tripolyphosphate (STPP), but

Table 5. United States Production of Industrial Chelating Agents[a]

Agent	Production, 10^3t/yr[b]	Price range[c] $/kg	Producers[d]
STPP	277 (241)	0.66–0.88	F, Mon, Oc, Ol, R-P
citric acid	143 (147)	0.88–1.98	HRC, Pfi
aminopolycarboxylic acids	104 (66)		C-G, D, WRG
30–40% solutions		0.66–1.98	
powders/crystals		3.31–7.94	
gluconic acid	7 (11)	0.77–1.32	A, B, Pfa, Pfi, PMP
glucoheptonic acid[e]	9 (8)	0.44–1.54	B, Pfa
organophosphonates	12 (16)	1.54–2.42	Ma, Mon

[a]Estimated for 1990; includes all forms of the compounds (50).
[b]Thousands of metric tons consumed per year given in parentheses.
[c]Depends on form of compound and size of shipment.
[d]F = FMC Corp.; Mon = Monsanto Co.; Oc = Occidental Petroleum Corp.; Ol = Olin Corp.; R-P = Rhone-Poulenc Inc.; HRC = Haarmann & Reimer Corp. (subsidiary of Bayer USA, Inc.); Pfi = Pfizer Inc.; C-G = Ciba-Geigy Corp.; D = The Dow Chemical Company; WRG = W. R. Grace & Co.; A = Akzo America Inc.; B = Belzak Corp.; Pfa = Pfanstiehl Laboratories, Inc.; PMP = PMP Fermentation Products, Inc.; Ma = Mayo Chemical Co.
[e]Glucoheptonic acid [*23351-51-1*], $C_7H_{14}O_8$.

only a small fraction of this product is used in chelation applications (see PHOSPHORIC ACID AND THE PHOSPHATES). Its primary chelating use is in water treatment and cleaning formulations. Most of the citric acid (qv) is also consumed in nonchelant applications in the food and beverage industry. Citric acid is used for its chelating properties mainly in cleaning applications where STPP is not suitable.

The aminopolycarboxylic acids are used principally as chelating agents, and a large proportion is used in water treatment and cleaning formulations. The data of Table 5 include nitrilotriacetic acid (NTA), most of which was exported.

Gluconates and glucoheptonates are largely interchangeable except in foods where the heptonates are prohibited. These compounds chelate polyvalent metals in strongly alkaline solution and are used in many ways, including metal cleaning, bottle washing, food service cleaning applications, electroplating, derusting, aluminum etching, and in concrete. Alkaline gluconate solutions dissolve ferric oxide.

Organophosphonates are similar to polyphosphates in chelation properties, but they are stable to hydrolysis and replace the phosphates where persistence in aqueous solution is necessary. They are used as scale and corrosion inhibitors (52) where they function via the threshold effect, a mechanism requiring far less than the stoichiometric amounts for chelation of the detrimental ions present. Threshold inhibition in cooling water treatment is the largest market for organophosphonates, but there is a wide variety of other uses (50).

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CHEMICAL CLEANING. See METAL SURFACE TREATMENTS.

CHEMICAL GROUTS. See SOIL STABILIZATION.

CHEMICAL VAPOR DEPOSITION. See ELECTRONIC MATERIALS; FILM DEPOSITION TECHNIQUES; THIN FILMS.

CHEMICALS IN WAR

Chemicals used in war fit into five categories: flame agents, incendiaries, smokes and obscurants, riot control agents, and toxic agents. Flame and incendiary agents are used to harass and inflict casualties, and to destroy structures and matériel. Smokes and obscurants are employed for screening, signaling, and target marking, in both offensive and defensive applications. Riot control agents are nonlethal